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NEUROPHARMACOLOGY AND THERAPEUTICS OF AF CHEMICALS

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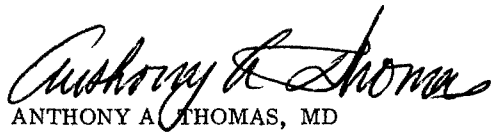

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In a continuing evaluation of mechanisms underlying convulsions produced by monomethylhydrazine (MMH) we have attempted to compare this response to seizures produced by a non-toxic, chronic experimental model of current interest in epilepsy (kindling). A series of studies were directed towards a comparison of 1) seizure susceptibility, 2) the protective effects of pyridoxine and 3) the therapeutic effects of thalamic lesions on both models. A significant correlation was obtained between MMH seizure latencies and

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initial afterdischarge thresholds for kindling in the same animals. Moreover, pyridoxine provided substantial protection against MMH seizures and a slight but consistent elevation of seizure thresholds with the kindling model. Finally, lateral thalamic lesions significantly reduced seizure susceptibility with both models. The physiological and therapeutic implications of these findings are discussed.

PREFACE

This research was initiated by the Toxicology Branch, Toxic Hazards Division, Aerospace Medical Research Laboratory, under Project 2312. Experiments were performed from February 1, 1979 to January 31, 1980 under Contract AF F33615-79-C-0506 by the Department of Anatomy and Brain Research Institute, School of Medicine, University of California, Los Angeles, California 90024.

The experiments were conducted by M. B. Sterman, Ph.D. and M. N. Shouse, Ph.D. of the Veterans Administration Medical Center, Sepulveda, California 91343 and M. D. Fairchild, Ph.D. of the Veterans Administration Medical Center, Long Beach, California 90804. Kenneth C. Back, Ph.D. was contract monitor for the Aerospace Medical Research Laboratory.

NEUROPHARMACOLOGY AND THERAPEUTICS OF AF CHEMICALS

INTRODUCTION

Studies in our laboratory have shown clearly that seizures resulting from hydrazine derivatives are initiated in subcortical structures. Specifically, we have found that the first evidence of seizure discharge following exposure to both unsymmetrical dimethylhydrazine (UDMH) and methylhydrazine (MMH) is in limbic and striatal structures (figures 1 and 2). This activity is then propagated to neocortex leading to generalized convulsions. Our objectives involve a continuing effort at elucidation of the mechanism of these seizures and the corresponding development of appropriate therapeutic strategies. However, the study of mechanisms is made difficult by the complications resulting from other components of toxic response which can, in fact, be differentiated from seizure response (Sterman et al., 1969; Sterman and Kovalesky, 1979). Moreover, except for the possible disturbance of inhibitory transmitter synthesis related to the uptake of endogeneous pyridoxine (Clark et al., 1968; Schlesinger and Uphouse, 1972; Wood and Peesker, 1974), epileptologists have shown little interest in the convulsive properties of these substances.

The initiation of hydrazine induced seizures in limbic structures, however, suggests some similarity to one of the major human epileptic seizure types, those classified as complex-partial or psychomotor (Gastaut, 1970; Brazier, 1973). Additionally, this fact could relate the underlying seizure mechanism to that producing seizures in an extensively studied, chronic seizure model of limbic epilepsy known as kindling. In animals daily, single pulses of electrical stimulation delivered to limbic structures through surgically placed electrodes have been shown to produce localized electrical afterdischarge which gradually spreads to adjacent and contralateral tissues and then to cortex, leading eventually to generalized seizures (Goddard et al., 1969; Racine, 1972 and others). In the cat this process requires 15-35 days for the reliable elicitation of seizures (Wada and Sato, 1974; Shouse and Sterman, 1980b).

In the present study we were interested in further exploring possible similarities between seizures resulting from acute exposure to MMH and those developing gradually with basolateral amygdala kindling. An established link between these two seizure producing manipulations could facilitate our understanding of the mechanisms responsible for MMH induced seizures and may, additionally, attract interest in this compound among epileptologists. Towards this end, three experiments have been conducted. The first sought simply to compare seizure latencies after MMH exposure to initial afterdischarge thresholds with amygdala stimulation in the same animals. A second examined the protective capacity of administered pyridoxine in both of these seizure models. Finally, in a third study we sought to test the effects of subcortical lesions known to raise thresholds for MMH seizures on the development of kindled seizures.

METHODS AND RESULTS

EXPERIMENT #1: COMPARISON OF MMH SEIZURE LATENCIES AND AMYGDALA STIMULATION AFTERDISCHARGE THRESHOLDS.

Eight adult cats weighing between 3.07 and 6.02 kg were used. Under sodium

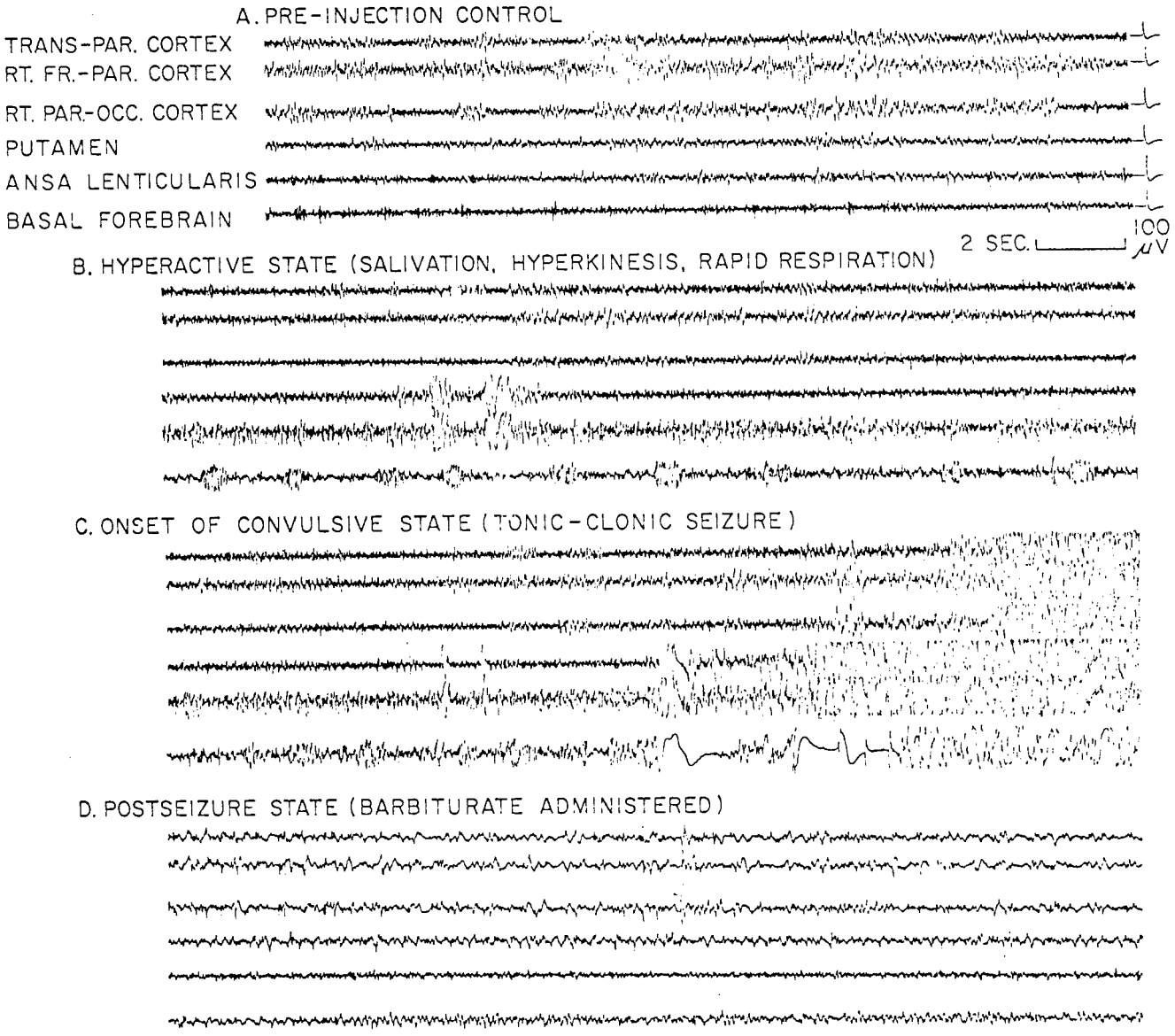

Figure 1. Polygraphic recordings of cortical and subcortical electrical activity in a cat before and at various stages after intraperitoneal injection of 30 mg/kg UDMH. Note that interictal and ictal activity is seen first in striatal and limbic structures (from Fairchild and Sterman, 1964).

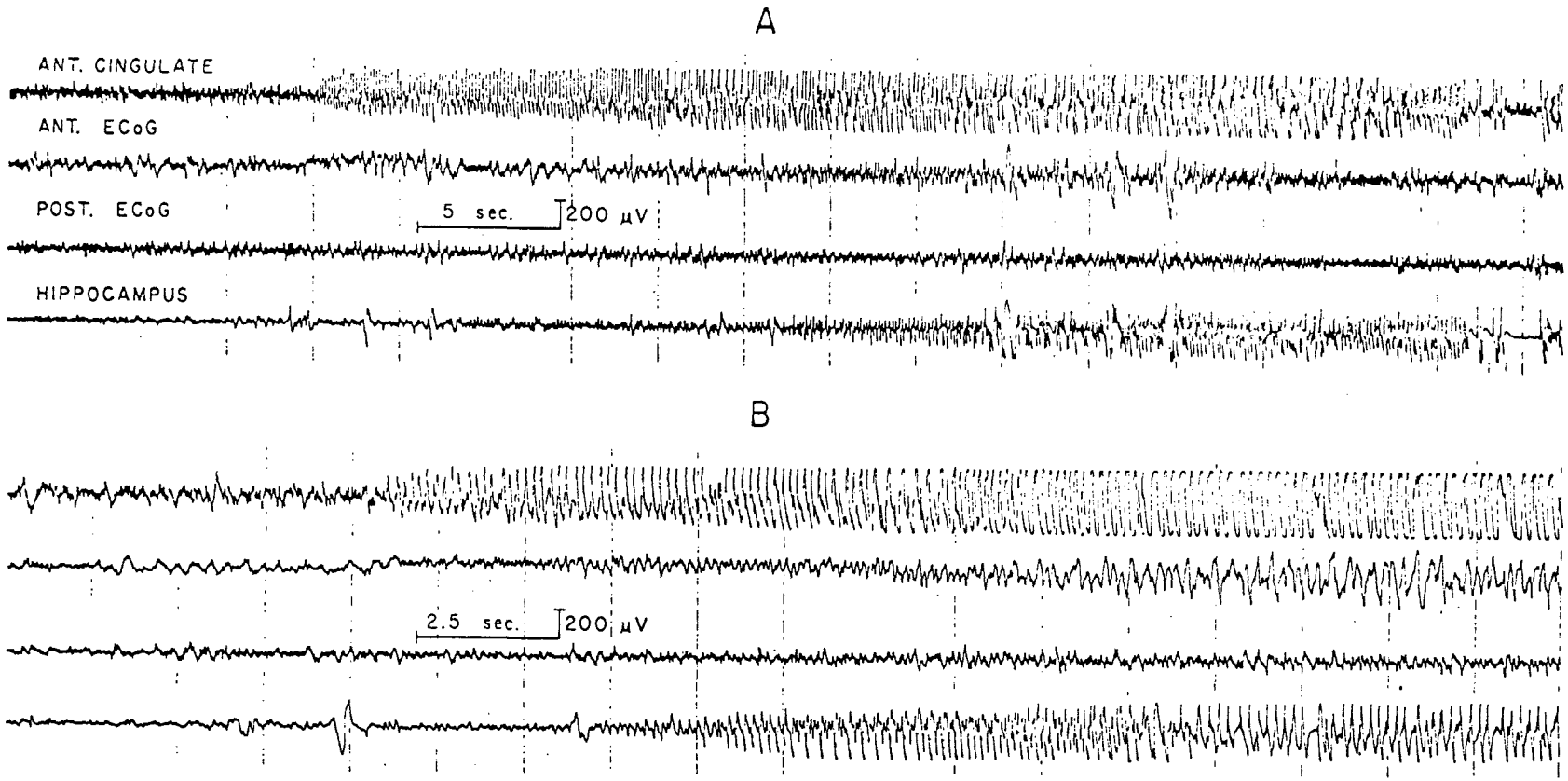

Figure 2. Polygraphic tracings obtained just prior to generalized seizures in a cat given a convulsive dose of UDMH. Note that seizure discharge is first seen in anterior cingulate gyrus and hippocampus (limbic structures) and is then propagated to anterior and posterior cortical recording leads. Similar findings have been obtained with MMH (from Goff et al., 1967).

pentobarbital anesthesia (35 mg/kg, i.p.), screw electrodes were implanted bilaterally over the sensorimotor cortex (A23, L8, 10) and tripolar deep electrodes were implanted bilaterally in the basolateral amygdala (A11, L9.0, 9.5, 10; H -5.5, -6.0, -5.5). Stereotaxic coordinates were obtained from the atlas of Snyder and Niemer (1961).

After a 2-week postoperative recovery, a convulsant dose (10 mg/kg, diluted in normal saline) of MMH (Matheson, Coleman and Bell, Norwood, Ohio, MW = 46.07 g/mol, sp.gr = 0.852) was administered and the animal was placed in a standard recording chamber for monitoring. All prodromal behaviors were recorded as well as seizure latencies measured in minutes postinjection to the onset of generalized tonic-clonic convulsions. Seizures were terminated in the tonic phase with an anesthetic dose of pentobarbital. The animal recovered in the experimental chamber and was returned to the home cage.

A minimum of 2 weeks intervened between the MMH trial and the determination of afterdischarge thresholds. Procedures for establishing these thresholds were described previously (Shouse and Sterman, 1979a; 1980a). Basically, 1 sec trains of biphasic square waves (60 Hz, 1 ms pulse) of 100μA were administered on the first day through a central amygdala electrode referenced to the skull (Grass S-8 stimulator). On day 2, 200μA was administered and thereafter stimulus intensity was increased by 200μA each day until afterdischarge was observed. Stimulation intensities were then decreased by 100μA until no afterdischarge appeared. Threshold was set at the minimum stimulation within 100μA necessary to elicit a unilateral afterdischarge response. Polygraphic recordings of sensorimotor cortex and amygdala bilaterally were obtained for the 10-min period before and after each stimulation, and the impedance of each subcortical electrode was determined with a Grass impedance meter after threshold was established. Finally, MMH and afterdischarge tests were conducted between 0800 and 1200 h in all animals.

MMH seizure latencies and afterdischarge thresholds are presented in Table 1 together with the gender, weight, and impedance of amygdala electrodes for each animal. Two types of statistical analyses were carried out on these data. First, Pearson product moment correlations were computed on all pairs or ordinal variables in the eight animals. The relationship between MMH latencies and afterdischarge thresholds was statistically significant ($r = 0.74$, $p<0.025$). Correlations between either index of seizure threshold and the remaining variables were nonsignificant.

Additional statistical evaluation was conducted on the basis of the distribution of MMH latencies. The median seizure latency for this group of animals was computed as 61 min, and, on the basis of that value, animals were divided according to high or low MMH seizure latency. Animals with MMH seizure latencies below this value had a mean latency of 54.24 ± 2.06 min. Animals with MMH seizure latencies above this value had a mean delay of 65.75 ± 3.5 min. The difference between these values was significant on a simple analysis of variance ($F = 32.06$, $p<0.01$).

Similar trends were evidenced in afterdischarge thresholds. Animals with low MMH latencies showed the lowest afterdischarge thresholds, which averaged

Table 1. Latencies to monomethylhydrazine (MMH)-induced seizures and after-discharge thresholds of eight cats together with the gender, weight, and impedances of the stimulated amygdala electrode.

Animal No.		MMH latency (min)	After-discharge threshold (μA)	Gender	Weight (kg)	Impedance of stimulated amygdala electrode (kΩ)
			Low MMH Latencies			
1		52	700	M	5.22	30
2		54	700	M	4.18	45
3		54	700	F	3.07	15
4		57	300	F	6.02	25
	$\bar{x}$	54.25	600		4.62	28.75
	SD	2.06	200		1.28	12.5
			High MMH Latencies			
5		62	1400	M	4.04	40
6		64	1200	M	5.34	7
7		67	1200	M	5.63	30
8		70	1200	F	3.86	25
	$\bar{x}$	65.75	1250		4.72	25.5
	SD	3.5	100		0.90	13.8

600 ± 200μA. In contrast, animals with high MMH latencies displayed significantly higher afterdischarge thresholds, with a mean of 1250 ± 100μA ($F = 33.8$, $p<0.01$). Thus, animals with the shortest MMH latencies also showed the lowest afterdischarge thresholds, and vice versa. These differences were not accounted for by the gender, weight, or target electrode positions of individuals because all three factors were equally distributed between the two populations. Electrode impedances obtained at the time afterdischarge thresholds were established did not differ significantly between these groups, indicating that this factor was not responsible for the sizable discrepancies in afterdischarge thresholds.

EXPERIMENT #2: EFFECTS OF PYRIDOXINE ON MMH AND KINDLED SEIZURES.

A second group of eight adult cats was employed in this study. These animals were prepared surgically in a manner identical to that described in the first experiment. Following recovery from surgery, initial afterdischarge thresholds only were established in four animals, as described above, the remaining animals were kindled normally (figure 3) with seizure thresholds established after stage 6 convulsions were elicited (Wada and Sato, 1974; Shouse and Sterman, 1980b). The experimental design employed an A_1 B_1 A_2 design in which MMH latencies ($n = 8$) and either afterdischarge threshold ($n = 4$) were examined in the same animals under three conditions: 1) an initial baseline or untreated condition (A_1); 2) following 20 mg/kg intramuscular injections of pyridoxine (B_1) and; 3) a final baseline condition (A_2). Two weeks intervened between each phase due to the necessity of a recovery period following pentobarbital injections used to terminate MMH trials.

Afterdischarge and kindled seizure thresholds before, during and after pyridoxine treatment are presented for both subgroups in Table 2. It can be seen that pyridoxine had no effect on afterdischarge threshold elicited in four kindled animals (A). In contrast, however, a small but consistent increase in kindled seizure thresholds was obtained in the four other animals during the period of pyridoxine treatment (B). This increase was statistically significant ($p=<.05$) from the final baseline condition.

Corresponding latencies to MMH induced convulsions in all eight animals are shown in Table 3. Initial baseline latencies in these animals were somewhat less consistent than in previous studies (Sterman, 1976) but the group mean value did not differ significantly from established norms. However, when tested with MMH after three days of pyridoxine treatment only one animal demonstrated convulsions within a five hour (300 min) designated observation period. Seven animals were completely protected against the convulsive effect of this compound. Latencies returned to baseline values during the final baseline test conducted two weeks after withdrawal from pyridoxine treatment.

EXPERIMENT #3: EFFECT OF LATERAL THALAMIC LESIONS ON MMH AND KINDLED SEIZURES.

A third set of 16 adult cats were employed in this study. The objective here was to compare the effects of lateral thalamic lesions (i.e., ventrobasal and reticularis nuclei) on the seizure inducing capacity of both MMH and kindling. In actuality, eight of these animals were studied previously in an experiment that showed a significant increase in seizure threshold (i.e., latency) to MMH exposure following thalamic lesions but not following control lesions in

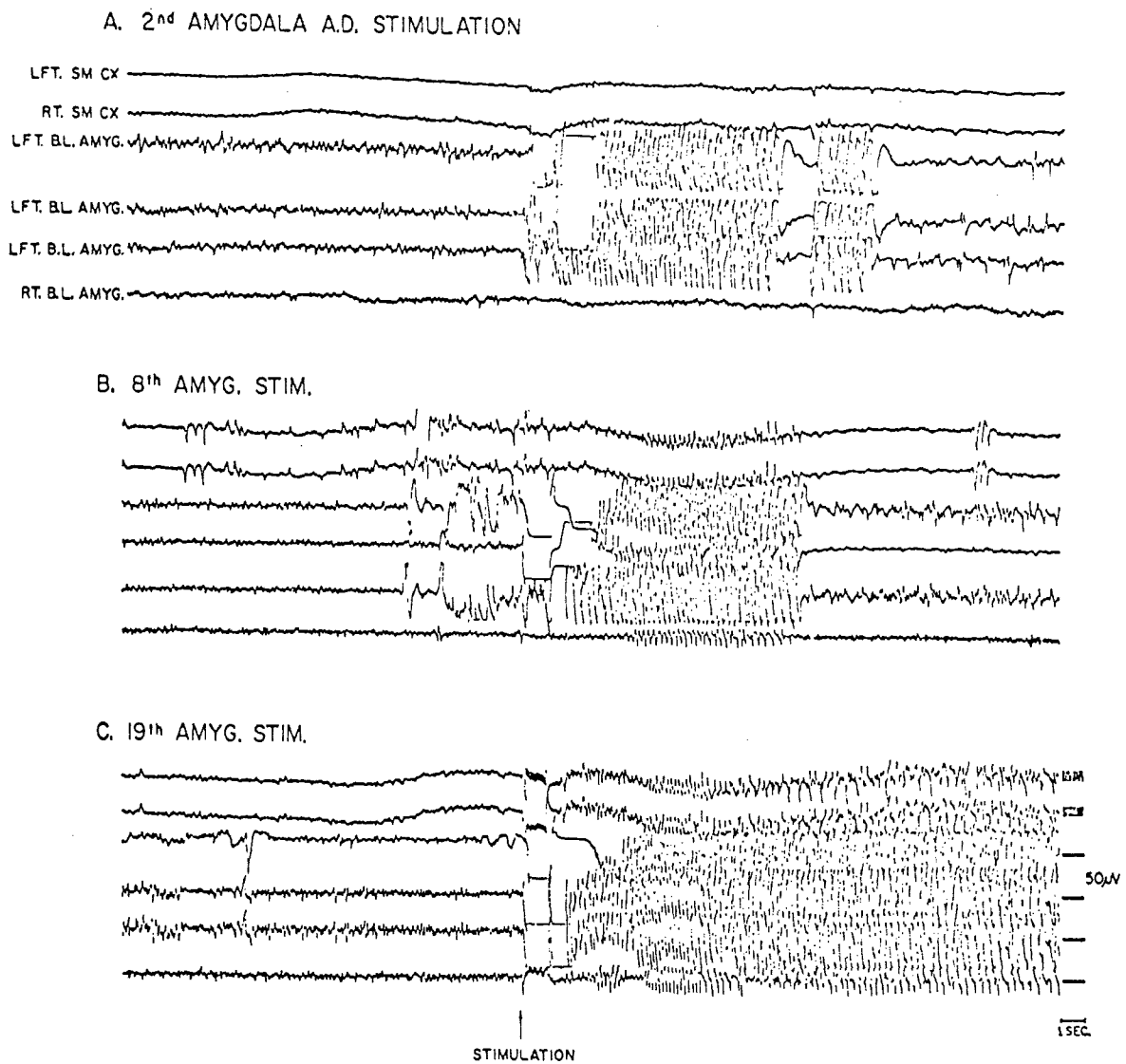

Figure 3. EEG tracings illustrating the spread of ictal discharge over the course of kindling. Initial stimulations produced afterdischarge in leads ipsilateral to the stimulating electrodes in left basolateral amygdala (A). During subsequent stimulations, ictal discharge spread to the contralateral amygdala and to neocortical (sensorimotor cortex) leads (B) and eventually produced a generalized tonic-clonic convulsion (C).

Table 2. Comparison of afterdischarge thresholds and kindled seizure thresholds in two groups of cats (n = 4 each) before, during and after treatment with pyridoxine hydrochloride.

Experimental Groups		STIMULATION INTENSITY (μA) Initial Baseline	Pyridoxine (20 mg/kg)	Final Baseline
A. Afterdischarge threshold				
Cat No. 1		450	500	450
2		200	200	200
3		150	150	150
4		200	150	200
	$\bar{X}$	250 μA	250 μA	250 μA
B. Kindled seizure threshold				
Cat No. 5		150	200	150
6		175	250	225
7		150	175	125
8		400	450	450
	$\bar{X}$	218.75 μA	268.75 μA*	237.5 μA

*$p = <.05$

Table 3. Comparison of latency to generalized seizures following exposure to monomethylhydrazine in eight cats before, during and after treatment with pyridoxine hydrochloride.

	LATENCY TO CONVULSION IN MIN. (MMH, 10 MG/KG)		
CAT NO.	INITIAL BASELINE	PYRIDOXINE (20 MG/KG)	FINAL BASELINE
1	125	300*	92
2	45	300	58
3	71	300	110
4	57	300	88
5	75	93	96
6	64	300	56
7	104	300	63
8	70	300	100
$\bar{x}$	76.38	274.13*	82.88
SD	25.94	73.19	20.86

* 300 MIN. = NO SEIZURE

$p = <.05$

cerebellar white matter or pontine tegmentum (Shouse and Sterman, 1979b). The present study examined the effects of similar lesions on the development of kindled seizures. Accordingly, eight additional animals were prepared surgically for monitoring cortical and subcortical EEG activity and for kindling, as described above. Two sets of bipolar electrodes were also implanted stereotaxically into lateral thalamic nuclei on both sides in four animals (A = 9.0; L7.5; H+2.0) and into various hypothalamic sites in four others for eventual placement of electrolytic lesions.

Following recovery from surgery, these animals were adapted to an experimental recording chamber and two baseline 12-hour polygraphic recordings were obtained. After baseline measures were collected, initial afterdischarge thresholds were established, according to the procedure described in experiment #1. Once these thresholds were determined and an additional baseline polygraphic recording obtained, bilateral lesions were placed in lateral thalamic structures or in basal forebrain structures, and daily kindling stimulation was begun. Daily amygdala stimulation was continued until generalized convulsions were obtained. If convulsions were not elicited after 75 days of kindling stimulation in a particular animal the experiment was terminated for that animal. At the end of the experiment, each animal was sacrificed with an overdose of barbiturate and the brain removed for histological verification of stimulation and lesion sites.

A comparison of minutes to generalized seizures following acute MMH exposure and days to generalized seizures following chronic kindling stimulation in animals with control and thalamic lesions is presented in Table 4. As previously reported, lateral thalamic lesions significantly prolonged latencies to generalized seizures following convulsive MMH exposure. One of these animals, in fact, failed to develop any seizures. Control lesions, however, produced no changes from normative values established previously (Sterman et al., 1969: Sterman, 1976).

The effect of thalamic and hypothalamic lesions on latency to kindled seizures was more complicated. As noted above several studies have shown that 15-35 stimulation days are required to elicit generalized seizures with basolateral amygdala stimulation (Wada and Sato, 1974; Shouse and Sterman, 1980). The data presented in Table 4 show that lateral thalamic lesions significantly delayed this effect. Two animals in this group also failed to kindle during the 75 stimulations criterion period. In contrast, animals with control lesions did not differ significantly from the normal. Thus, lateral thalamic lesions protected against both MMH and kindled seizures.

DISCUSSION

Each of the studies reported here has indicated some relationship between the seizure inducing properties of MMH exposure and amygdala kindling stimulation. Afterdischarge thresholds with amygdala stimulation were lowest in animals showing the shortest latency to MMH induced seizures and vice versa. Pyridoxine protected animals against both of these convulsive manipulations but was clearly more effective with MMH. Finally, lateral thalamic lesions interfered with the development of seizures in both of these models. Thus, in addition to a common initiation of seizures in limbic structures these two completely different experimental seizure models show other similarities.

TABLE 4. Comparison of seizure response to MMH and kindling stimulation in two groups of cats with subcortical lesions. Control lesions in MMH subgroup were in cerebellum and pontine tegmentum while those in kindled subgroup were in hypothalamus. Thalamic lesions were in ventrobasal and reticularis nuclei.

Group	Latency to MMH Seizures (min)	Latency to Kindled Seizures (days)
1. Control Lesions		
1	90	11
2	86	12
3	60	19
4	45	23
$\bar{X}$	70.25	16.25
2. Thalamic Lesions		
1	300*	46
2	280	63
3	218	75*
4	121	75*
$\bar{X}$	229.75	64.75

* = no seizures

Although the correspondence between MMH seizure latencies and afterdischarge thresholds was not perfect, a statistically significant relationship between these two indices was established. Both correlation coefficients and analyses of variance indicated that animals with prolonged MMH latencies also showed significantly higher afterdischarge thresholds; similarly, shorter MMH latencies accompanied lower afterdischarge thresholds. These outcomes could not be attributed to differences in obvious population parameters such as gender, weight, electrode site or impedance. The fact that any relationship was found between these two seizure-inducing experimental procedures suggests that intrinsic differences in seizure susceptibility exist in a given population of animals. On the other hand, the differences in seizure susceptibility obtained here may bear a direct relation to a common pathogenetic mechanism of two apparently dissimilar methodologies.

The administration of pyridoxine produced a substantial protective effect against seizures resulting from acute exposure to MMH. While the corresponding effect in kindled animals was clearly less impressive, it should be kept in mind that these animals were already chronically epileptic at the time of testing. Accordingly, it would be interesting to examine the potential protective effects of pyridoxine using a chronic study approach, with blood levels maintained throughout the process of daily kindling stimulation. Other studies have, in fact, reported progressive changes in neurotransmitter substances during the course of kindling in rats (Sato and Nakeshima, 1975; Engel and Sharpless, 1977).

The fact that lateral thalamic lesions provided comparable protection against MMH and kindled seizures is subject to several interpretations. It suggests that the propagation of ictal activity from limbic structures to sensorimotor cortex is at least partially mediated by thalamocortical pathways in both instances, thereby implying a common mechanism at this level of seizure development. However, this protective effect is also consistent with a growing body of literature indicating thalamic mediation of generalized motor seizures in other animal models (Kusske et al., 1972; Van Stratten, 1975; Pellegrini et al., 1979) and in human epilepsy as well (Gillingham et al., 1976; Mullen et al., 1977). Thus, the protection noted may reflect a more general aspect of seizure development rather than a link between these two seizure models.

Notwithstanding the complex nature of seizure pathology, the findings reported here support the possibility of a relationship between MMH and kindled seizures. The implications of this conclusion in terms of therapeutic strategies for MMH exposure could be significant. For example, a number of studies have shown that animals can be protected from kindled seizures with certain anticonvulsant compounds not previously tested as therapeutic agents for MMH. Among these are phenobarbital, carbamazepine and diazepam (Wise and Chinaman, 1974; Racine et al., 1976; Wada, 1977). With non-lethal exposure, barbiturates can also suppress seizures resulting from MMH. As a part of our present contract we are now examining the physiological characteristics of the other two compounds, as well, in preparation for testing their therapeutic potential with MMH. Furthermore, because of the intensive study of kindling currently underway among epileptologists, this link would make other therapeutic possibilities as well as new evidence concerning mechanism from kindling studies useful also for the study of MMH.

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